BIOGRAPHICAL SKETCH

Provide the following information for the senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: James L. Gulley, MD, PhD, FACP

eRA COMMONS USER NAME (credential, e.g., agency login): gulleyj

POSITION TITLE: Chief, Genitourinary Malignancies Branch, CCR; Head, Clinical Immunotherapy Section, GMB, CCR; Director, Medical Oncology Service, CCR, NCI

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YY	FIELD OF STUDY
Southern College of SDA, Collegedale, TN	B.A.	1987	Chemistry
Loma Linda University, Loma Linda, CA	Ph.D.	1994	Microbiology
Loma Linda University, Loma Linda, CA	M.D.	1995	Medicine
Emory University, Atlanta, GA		1998	Internal Medicine
National Cancer Institute, Bethesda, MD		2000	Medical Oncology

A. Personal Statement

As Chief of the Genitourinary Malignancies Branch and Head of the Clinical Immunotherapy Section, I oversee one of the busiest clinical programs in the Center for Cancer Research. We enroll about 250–300 patients a year on our therapeutic clinical trials, largely studies of immunotherapy. My group has focused on T cell-poor tumors such as prostate cancer and the development of strategies to optimize immunological approaches for effective therapy. Our overriding strategy has been to concentrate on opportunities to focus the immune response through vaccines or adoptive cellular therapy and then facilitate effector function of those activated immune cells within the tumor microenvironment through approaches including immune checkpoint modulation. I have been involved in the clinical development of Prostvac from the first-in-human studies at the CCR through a completed 1,297-subject phase III clinical trial that I led. Unfortunately, there was no improvement in overall survival seen with vaccine alone. I am honored to lead an international first-in-human study of avelumab, an immune checkpoint modulator initiated at the CCR, that has been rapidly taken into phase III testing based on our work with an approval in April for Merkel cell carcinoma and bladder cancer. I am most enthusiastic about our ongoing and planned multiple CCR-originated multicenter studies of immune checkpoint combination approaches (e.g., vaccine and immune checkpoint inhibitor).

B. Positions and Honors

Positions and Employment

1995 – 1998	Resident, categorical internal medicine, Emory University, Atlanta, GA
1998 – 2000	Fellow, Medical Oncology, National Cancer Institute, NIH, Bethesda, MD
2000 – 2001	Senior Fellow, Medical Oncology, National Cancer Institute, NIH, Bethesda, MD
2004 – 2012	US FDA Advisory Committee, Immunology Devices Panel
2001 – 2013	Director, Clinical Immunotherapy Group, LTIB, NCI, NIH, Bethesda, MD
2011 – 2013	Deputy Chief, LTIB, Center for Cancer Research (CCR), NCI, NIH, Bethesda, MD
2011 – 2013	Senior Investigator, Medical Oncology Branch, CCR, NCI, NIH
2013 – present	Director, Medical Oncology Service, CCR, NCI, NIH
2013 – present	Chief, Genitourinary Malignancies Branch, CCR, NCI, NIH
2013 – present	Head, Immunotherapy Section, Genitourinary Malignancies Branch, NCI, NIH

Honors (selected)

2003 NCI Group Merit Award, "For Major Contributions to the Field of Cancer Immunotherapy."
2008 US FDA Advisory Committee Service Award, "In recognition of distinguished service, Immunology Devices Panel, March 2004–February 2008."
2009 NIH Group Merit Award "For achievements in the field of therapeutic cancer vaccines, from vaccine design to science-driven clinical studies, as an outstanding translational program."
2010 Presidential Early Career Award for Science and Engineering "For randomized, controlled studies using novel, recombinant vaccines to reduce the progression of prostate and other cancers and increase survival."
2011 NIH Group Merit Award "For making enormous strides in the treatment of several different stages of prostate cancer."
2012 Alumnus of the Year Award "Honoring outstanding contributions to the advancement of the medical profession and cancer patient care," presented by the Southern Adventist University Alumni Association.
2012 CCR Senior Staff's Top Science Advances of FY2012 for "Ipilimumab and a poxviral vaccine targeting prostate-specific antigen in metastatic castration-resistant prostate cancer: a phase 1 dose-escalation trial." *Lancet Oncol*. 2012 May;13(5):501-8.
2013 Honored Alumnus Award, presented by the Alumni Association, School of Medicine, Loma Linda University at their Annual Gala.
2014 Federal Technology Transfer Award
2015 Federal Laboratory Consortium Mid-Atlantic Regional Award for Excellence in Technology Transfer, for "Development of first immunotherapy to treat chordoma, a rare bone cancer."
2016 Federal Laboratory Consortium Excellence in Federal Technology Transfer Award, a national award for "Development of first immunotherapy to treat chordoma, a rare bone cancer."
2016 NCI Director's Award "For outstanding contributions leading to translation of CCR co-developed immunotherapies into multiple phase III studies, and for helping to pioneer the field of immunogenic intensification."
2016 NIH Director's Award for CCR Science Board, "For exceptionally insightful and diligent guidance, oversight, and leadership in developing scientific projects that will shape the future of the NCI intramural program."

Serve on 8 **editorial boards**, including *Molecular Cancer Therapeutics* (an AACR Journal), *Prostate Cancer*, *The Oncologist* (Associate Editor), Journal of Immunotherapy for Cancer (SITC Journal, Section Editor) and *JNCI Journal of the National Cancer Institute* (Associate Editor)

C. Contribution to Science

A novel off-the-shelf therapeutic vaccine for prostate cancer

Prostate cancer is the most commonly diagnosed lethal cancer in men and the second most common cause of cancer-related mortality. In 2010 the FDA approved a costly, apheresis-derived therapeutic vaccine for the treatment of prostate cancer. However, our off-the-shelf approach is logistically simpler. I have successfully translated a vaccine strategy developed within the CCR into a phase I, a phase II, and now an ongoing phase III clinical trial in prostate cancer. The initial successes of this technology have led to a significant investment in developing poxviral-vector therapeutic vaccines, with an ongoing industry-sponsored phase III study and a planned trial with a similar vaccine targeting other cancers. A recent multicenter, randomized phase II trial that I helped to design employed a recombinant poxviral vaccine developed at the CCR. This trial provided evidence of enhanced median overall survival (OS) (P = 0.0061) in patients with metastatic castration-resistant prostate cancer (mCRPC). A concurrent study that I ran at the CCR employed the identical vaccine in mCRPC to investigate the influence of GM-CSF with vaccine and the influence of immunologic and prognostic factors on median OS. Median OS was 26.6 months, and

patients with greater PSA-specific T-cell responses showed a trend (*P* = 0.055) toward enhanced survival. There was no difference in T-cell responses or survival in cohorts of patients receiving GM-CSF vs. no GM-CSF. Patients with a Halabi-predicted survival of < 18 months (median predicted: 12.3 months) had an actual median OS of 14.6 months, while those with a Halabi-predicted survival of ≥ 18 months (median predicted: 20.9 months) will meet or exceed 37.3 months, with 12/15 patients living longer than predicted (*P* = 0.035). Treg suppressive function decreased following vaccine in patients who survived longer than predicted and increased in patients who survived less than predicted. This hypothesis-generating study provides evidence that patients with more indolent mCRPC may benefit most from vaccine therapy. Based on the results of these two studies, I am leading a global, 1,297-patient, randomized, controlled, CRADA partner-sponsored phase III study that completed accrual in January 2015. Other vaccines against novel tumor-associated targets with this and other platforms are in development. *Prostate* 53:109-17, 2002; *J Urol* 178(4 Pt 1):1515-20, 2007; *Cancer Immunol Immunother* 59:663-74, 2010; *J Clin Oncol* 28(7):1099-105, 2010; *Cancer Immunol Res* 2:133-41, 2014.

Combining immunotherapy with standard-of-care agents

Recent data from the CCR suggest that certain standard-of-care agents (radiation, chemotherapy, small molecule inhibitors, etc.) can alter the tumor phenotype, making it easier for the immune system to recognize and kill tumor cells. Murine studies suggested dramatically improved outcomes with these combination therapies compared to either modality alone. These findings led to several clinical trials. Two combination trials in prostate cancer suggest an improvement in PFS: Quadramet ± Prostvac vaccine (1.7 vs. 3.7 months, *P* = 0.035, HR 0.48) in 44 patients with disease metastatic to bone (trial results being written), and flutamide with or without Prostvac vaccine (preliminary, 108 vs. 192 days) in 41 patients with nonmetastatic castration-resistant disease (trial recently completed accrual). A breast cancer trial comparing docetaxel ± Panvac vaccine in 48 patients with metastatic disease shows a trend toward improved PFS favoring the combination (3.8 vs. 6.6 months, *P* = 0.12, HR 0.67, *Oncotarget*, 2016). Rationally designed combination studies have the potential to significantly expedite analysis in proof-of-concept efficacy studies (phase II) and may also improve patient outcomes over standard therapy alone. *JAMA Oncol* 1(8):1087-95, 2015. *Oncotarget* 7(42):69014-23, 2016.

Immune checkpoint inhibitors

In 2017, the American Society of Clinical Oncology (ASCO) once again named immunotherapy as the advance of the year, due in part to the rapid, profound, and durable responses seen with immune checkpoint inhibitors. CCR preclinical studies suggested synergy between vaccine and CTLA-4 blockade. I was the PI of a study combining a CCR-developed vaccine (PSA-TRICOM) with ipilimumab, an anti-CTLA-4 antibody. Up to 10 mg/kg of ipilimumab was safely administered with PSA-TRICOM, and immune-related adverse events were similar in proportion and grade to those previously reported with ipilimumab alone. Furthermore, while the median predicted survival was ~ 18 months based on a validated nomogram, actual median OS was > 34 months in this phase I study. This compares favorably to OS data with ipilimumab alone, but a randomized study would be required to validate these hypothesis-generating findings. Recent clinical data on PD-1 or PD-L1 inhibition have accelerated interest in the field of immunotherapy. I am the coordinating PI of a phase I dose-escalation study of avelumab, the only anti-PD-L1 antibody designed to not only antagonize PD-L1, but to initiate antibody-mediated cellular cytotoxicity (ADCC). This first-in-human international study of this agent, sponsored by our CRADA partner EMD Serono, has demonstrated dramatic prolonged responses, including a high proportion of patients with thymic epithelial malignancies but with objective responses seen in a variety of cancers. Our data also demonstrated no impact of ADCC on immune cells, which can also express PD-L1 (albeit often at lower levels than tumor cells). Based on these clinical data, a randomized controlled phase III trial was recently initiated in lung cancer. Furthermore, avelumab has been given breakthrough designation by the FDA, based in part on our work, and approval is expected soon. However, immune checkpoint inhibition requires an underlying antitumor immune response that it can unleash. In prostate cancer, the level of activated immune cells within the prostate is limited. Thus, combining vaccine with PD-L1 blockade is a rational immunotherapeutic approach. To explore this possibility, we have designed a study with our CRADA partner Bavarian Nordic and their new partner, BMS, for a combination study of PSA-TRICOM (developed at the CCR) and immune checkpoint inhibition. We have also initiated several multicenter studies with an anti-PD-L1/TGF-β Trap (first-in-human with dose escalation only at CCR), avelumab and

NHS-IL12 (a tumor-targeted IL-12) and nivolumab with or without a CEA/MUC1 vaccine (CV-301) in a randomized study in non-small cell lung cancer. *Lancet Oncol* 13:501-8, 2012; *J Clin Oncol* 32(10):986-8, 2014; *Cancer Immunol Immunother* 63:407-18, 2014. *Lancet Oncol* 18(5):599-610 2017*, Lancet Oncol* 18(5):587-598 2017 *J Clin Oncol* 1;35(19):2117-2124 2017.

List of Published Work in MyBibliography (>200 publications)
https://www.ncbi.nlm.nih.gov/sites/myncbi/james.gulley.1/bibliography/47943666/public/?sort=date&direction=ascending

D. Research Support (all support for intramural studies comes from the Center for Cancer Research (CCR), NCI)

Clinical Protocols (Selected from >100 Total Trials; Chair or PI for >30)

Intramural (CCR) Studies

1. Associate Investigator: NCI 00-C-0137 A randomized phase II study of either immunotherapy with a regimen of recombinant pox viruses that express PSA/B7.1 + adjuvant GM-CSF and IL-2 or hormone treatment with nilutamide in patients with hormone refractory prostate cancer and no radiographic evidence of disease.
2. Protocol Chair: NCI 00-C-0154 A randomized phase II study of a PSA-based vaccine in patients with localized prostate cancer receiving standard radiotherapy.
3. Associate Investigator: NCI 02-C-0218 A pilot trial of concurrent docetaxel and a pox vector PSA vaccine followed by docetaxel in metastatic androgen independent prostate cancer.
4. Associate Investigator: NCI 03-C-0005 A pilot study of sequential vaccinations with recombinant vaccinia-CEA(6D)-TRICOM, and recombinant fowlpox-CEA(6D)-TRICOM (B7.1/ICAM-1/LFA-3) with sargramostim (GM-CSF), in conjunction with standard adjuvant chemotherapy in high-risk breast cancer patients.
5. Principal Investigator: NCI 03-C-0176 A phase I/II pilot study of sequential vaccinations with rFowlpox-PSA(L155)-TRICOM (PROSTVAC-F/TRICOM) alone, or in combination with rVaccinia-PSA(L155)-TRICOM (PROSTVAC-V/TRICOM), and the role of GM-CSF, in patients with prostate cancer.
6. Principal Investigator: NCI 04-C-0246 An open label pilot study to evaluate the safety and tolerability of PANVAC-V (vaccinia) and PANVAC-F (fowlpox) in combination with sargramostim in adults with metastatic carcinoma.
7. Principal Investigator: NCI 05-C-0017 A phase I feasibility study of an intraprostatic PSA-based vaccine in men with prostate cancer and local failure following radiotherapy or cryotherapy or clinical progression on androgen-deprivation therapy in the absence of local definitive therapy.
8. Principal Investigator: NCI 05-C-0167 Phase I trial of a PSA-based vaccine and an anti-CTLA-4 antibody in adults with metastatic androgen-independent prostate cancer.
9. Principal Investigator: NCI 05-C-0229 A randomized pilot phase II study of docetaxel alone or in combination with PANVAC-V (vaccinia) and PANVAC-F (fowlpox) in patients with metastatic breast cancer.
10. Principal Investigator: NCI 07-C-0106 A randomized phase 2.5 study of ^{153}Sm-EDTMP (Quadramet) with or without a PSA/TRICOM vaccine in men with androgen-insensitive metastatic prostate cancer.
11. Principal Investigator: NCI 07-C-0107 A randomized phase II trial combining vaccine therapy with PROSTVAC/TRICOM and flutamide vs. flutamide alone in patients with androgen-insensitive, nonmetastatic (D0.5) prostate cancer.
12. Principal Investigator: NCI 07-C-0188 A double-blind randomized phase 2.5 trial of ONY-P1 vaccine vs. placebo in men with D0 prostate cancer following limited androgen ablation.
13. Associate Investigator: NCI 09-C-0101 An open label phase I study to evaluate the safety and tolerability of a vaccine (GI-6207) consisting of whole, heat-killed recombinant *Saccharomyces cerevisiae* (yeast) genetically modified to express CEA protein in adults with metastatic CEA-expressing carcinoma.

14. Associate Investigator: NCI 09-C-0139 A pilot study of vaccination with epitope-enhanced TARP peptide and TARP peptide-pulsed dendritic cells in the treatment of stage D0 prostate cancer.
15. Principal Investigator: NCI 11-C-0225 First in-human phase I trial of NHS-IL12 in patients with metastatic solid tumors
16. Associate Investigator: NCI 11-C-0247 A randomized phase II study of L-BLP25 in combination with standard androgen-deprivation therapy and radiation therapy for newly diagnosed, high-risk prostate cancer patients.
17. Principal Investigator: NCI 12-C-0056 An open-label phase I study to evaluate the safety and tolerability of GI-6301 vaccine consisting of whole, heat-killed recombinant *Saccharomyces cerevisiae* (yeast) genetically modified to express brachyury protein in adults with solid tumors.
18. Associate Investigator: NCI 13-C-0095 A phase II study of GI-6207 in patients with recurrent medullary thyroid cancer.
19. Associate Investigator: Phase II open-label trial of ipilimumab for metastatic Merkel cell carcinoma.
20. Associate Investigator: 13-C-0153 A phase II trial of enzalutamide in combination with PSA-TRICOM in patients with nonmetastatic castration-sensitive prostate cancer.
21. Associate Investigator: 13-C-0146 A randomized phase II trial combining vaccine therapy with PROSTVAC/TRICOM and enzalutamide vs. enzalutamide alone in men with metastatic castration-resistant prostate cancer.
22. Principal Investigator: 17C0007 Phase I/II study of PROSTVAC in combination with nivolumab and/or ipilimumab in men with prostate cancer.

Extramural Studies **(selected)**

1. Site Principal Investigator and Global Principal Investigator: BNIT-PRV-301; NCI 11-C-0262 A randomized, double-blind, phase III efficacy trial of PROSTVAC-V/F with or without GM-CSF in men with asymptomatic or minimally symptomatic metastatic, castration-resistant prostate cancer. *This international 1,297-subject overall survival endpoint study completed enrollment in Jan 2015.*

2. Coordinating (lead) PI: A phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of avelumab (MSB0010718C), a monoclonal anti-PD-L1 antibody, in subjects with metastatic or locally advanced solid tumors. *An international study that has enrolled over 1,700 patients internationally and over 125 at the NCI. This has led to 6 ongoing phase III studies and plans for multiple additional phase III studies. NCT01772004*

3. Coordinating (lead) PI: A phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of MSB0011359C in subjects with metastatic or locally advanced solid tumors with expansion to selected solid tumors. *An international study of a first-in-human anti-PD-L1/TGF-β Trap with multiple expansion cohorts. NCT02517398*

4. Coordinating (lead) PI: A phase Ib open-label, dose-finding trial to evaluate the safety, tolerability, and pharmacokinetics of avelumab in combination with M9241 (NHS-IL12) in subjects with locally advanced, unresectable, or metastatic solid tumors. *An international study of a first-in-human combination of a tumor-directed delivery of IL-12 with avelumab. NCT02994953*

5. Principal Investigator: A trial of CV301 in combination with nivolumab versus nivolumab alone in subjects with previously treated non-small cell lung cancer. *A multicenter randomized study to see if the combination of vaccine targeting CEA and MUC-1 combined with nivolumab can improve outcomes compared with nivolumab alone.*